Clinical Proceedings

of the

CHILDREN'S HOSPITAL

WASHINGTON, D. C.

MEDICAL LIBRARY
UNIVERSITY
JAN 23 1947
LIBRARY

VOL. II MARCH 1946 No. 4

Copyright, 1946, Children's Hospital

THE SUCCESSFUL USE OF ORAL PENICILLIN IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS

Case Report*

Frederic Gerard Burke, M.D.
Sidney Ross, M.D.
Bernard J. Walsh, M.D.
P. A. McLendon, M.D.

Recent reports in the literature indicate that cures may be effected in cases of subacute bacterial endocarditis when an adequate dosage of penicillin is administered. Following initial discouraging observations,[1] Loewe et al.[2] achieved successful results in 7 consecutive cases of subacute bacterial endocarditis using combined penicillin-heparin therapy. More recently Loewe[3] reported 75 per cent cures in 54 consecutive cases. Similarly, other authors[4, 5, 6, 7] observed successful therapeutic results in 50 to 75 per cent of cases (see table 1).

In all of these patients the parenteral route of administration of penicillin was used, including continuous intravenous and intramuscular, and intermittent intramuscular injections. Because of the difficulties concerned in this manner of treatment, the oral method of administration was thought to offer definite advantages. It was determined in a series of preliminary experiments[7] that adequate penicillin blood levels could be obtained when the drug is protected from the inactivating influence of the hydrochloric acid in the stomach. Penicillin concentrations obtained after the ingestion of 100,000 units of powdered sodium penicillin in a double gelatin capsule compared favorably and in some respects surpassed those obtained after the administration of 40,000 units given parenterally. Characteristic of the curves obtained after the oral administration of 100,000 units was the rapid appearance of large amounts of penicillin in the blood stream with the highest levels demonstrable in the first 30 to 90 minutes after ingestion, and the continued presence of therapeutic levels of penicillin for at least 3 hours. The ingestion of a second 100,000-unit capsule 3 hours after the first dose produced an incremental rise in the penicillin titer similar to the initial 3-hour curve. It seemed justified to conclude that when these capsules were administered every 3 hours, therapeutic concentrations of the drug were maintained constantly. The average maximum levels observed ranged between 1.24 and 2.48 Florey units. In a clinical evaluation of oral peni-

* This article appeared in full in the January issue of the Medical Annals of the District of Columbia and is reprinted with the permission of Mr. T. Wiprud.

MEDICAL LIBRARY

TABLE 1

AUTHOR	NO. OF CASES	DURATION OF INFECTION	SENSITIVITY TO PENICILLIN	DAILY DOSAGE	TOTAL DOSAGE	ROUTE OF ADMINISTRATION	DURATION OF TREATMENT	HEPARIN	RESULTS	FOLLOW UP
				units	*units*					
Loewe	54	1 week to 19 months	0.007–0.5	40,000–1,000,000	367,000–18,930,000	Continuous IV	not given	Used in all cases	74% recovery, 26% failures	2–15 months
Dawson and Hunter	20	1 to 15 months, average 2 months	0.008–0.14	40,000–500,000	830,000–36,700,000 average 6,700,000	Intermittent IM Continuous IV Continuous IM	10–103 days, average 30 days	Given in 16 cases. Other 4 cases did not receive it.	15 cases or 75% recovery, 3 cases or 15% died, 2 cases or 10% relapsed.	1–10 months, average 6 months
Keefer et al.	17	not given	not given	not given	240,000–1,760,000	not given	9–26 days	not given	10 cases or 59% no effect, 4 cases or 23% died, 3 cases or 18% improved, 2 cases or 12% relapsed.	not given

Meads, Harris and Finland	9	2 weeks to 6 months, average 2 months	0.011–0.031	90,000–480,000	1,860,000–5,900,000, average 4,600,000	Chiefly Intermittent IM	6–19 days, average 17 days	Given in 3 cases. Other 6 cases did not receive it.	66% recovery, 22% relapsed, 11% died.	1–10 months, average 5 months
Spink and Hall	8	not given	not given	4 patients 240,000, 4 patients not given	4 patients 4,200,000, 4 patients less than 1,000,000	IV every 12 hours	17 days	none	? 50% cured	not given
Paullin and McLoughlin	6	1 to 24 weeks, average 7 weeks	not given	200,000–300,000	2,800,000–4,500,000, average 3,700,000	Intermittent IM	14–20 days	none	50% cured	1–6 months

cillin[8, 9] it was found that ready cures of susceptible infections could be effected when this method of administration was employed. It was therefore deemed of singular interest to attempt to treat a case of subacute bacterial endocarditis with oral penicillin. To our knowledge the present case report represents the first successful treatment of bacterial endocarditis with oral penicillin.

Methods and Materials

The contents of an ampule containing 100,000 units of powdered sodium penicillin was transferred to a plain gelatin capsule (no. 1) which was moistened and sealed and in turn placed in a second capsule of the next larger size (no. 0). The double capsule containing the penicillin was then hardened by placing it in a solution of formaldehyde U.S.P. diluted 1:20 for 5 seconds followed by immersion in 95 per cent alcohol for 5 minutes. The purpose of the double capsule was to provide additional mechanical protection for the penicillin.

In 2 instances during the course of treatment penicillin levels were assayed at hourly intervals during consecutive 6-hour periods to determine whether the penicillin blood concentrations were in excess of the susceptibility range of the Streptococcus viridans organism. Penicillin content was assayed according to the method of Rammelkamp,[10] B. hemolyticus streptococcus 203 being used as the indicator organism. Blood samples after withdrawal were immediately placed in the icebox and were usually examined within 2 or 3 days.

Report of Case

M. P., an 11-year-old white girl, was seen on April 4, 1945 by one of us (B. J. W.) and a diagnosis of interventricular septal defect and probable subacute bacteria endocarditis was made. She was admitted to Children's Hospital the same day.

A heart murmur was first noted when she was 1½ months old. Cyanosis and dyspnea were not present at any time. Her development had been normal, and her past history was essentially negative. Four weeks prior to admission she complained of easy fatigability and copious night sweats, and a persistent fever with daily temperature elevations was observed.

Physical examination revealed a well developed and nourished adolescent female who appeared pale but not acutely ill. Her temperature was 103°F., respirations were 27, and the pulse rate 128. No petechiae were noted. The second left upper molar tooth was decayed and loose. A harsh, loud, systolic murmur with maximum intensity in the third and fourth interspaces about 2 cm. to the left of the sternum was present and was transmitted over the entire precordium. There was an intense systolic thrill in the area where the murmur was loudest. The spleen was not palpable and the remainder of the physical examination was negative. An electrocardiogram was normal. A roentgenogram of the chest showed moderate enlargement of the right and left ventricles.

Three blood cultures, taken on April 21, 22 and 24, showed the presence of 30, 44,

and 12 colonies respectively of Streptococcus viridans per c.c. of blood. The strain showed a sensitivity range to penicillin of from 0.05 to 0.1 Florey units.

Repeated sedimentation rates were very rapid, and hemograms gave evidence of a moderate degree of anemia. The temperature curve during the first 2 weeks under observation showed a daily rise between 100°F. and 103.4°F. A small painful red area appeared on the sole of the right foot on the tenth hospital day and was considered to be due to an embolus.

Specific therapy was started on April 29, 1945. Sodium penicillin was prepared in double gelatin capsules, and 100,000 units was given every 3 hours. Preliminary neutralization of the gastric acidity was obtained by the administration of 2 aluminum hydroxide tablets 15 to 30 minutes before each dose of penicillin. The patient was given a soft, fat-free diet with moderate limitation of fluids, and her feeding schedule was slightly changed so that at no time was the penicillin given simultaneously with a meal.

Eight hours after the initiation of oral penicillin the temperature fell from 102°F. to normal and remained normal thereafter except for a transient rise to 100°F. on the ninth day at the time of the extraction of her decayed tooth.

A blood culture obtained 12 hours after the start of treatment showed no growth, and daily blood cultures taken during the entire period of 2 weeks the patient received penicillin were negative. Penicillinase was added to the broth in one of these blood cultures and no growth was observed.

Penicillin serum levels were assayed at various intervals during the 2 weeks of therapy and adequate therapeutic amounts of the drug were always demonstrable in the peripheral blood. As will be noted in chart 1 the effect of a successive dose of penicillin was to produce an incremental rise in the existing titer and so maintain a constant therapeutic blood level. The patient received 100,000 units of penicillin as a single dose every 3 hours for 14 days, a total dose of 11,200,000 units. No toxic symptoms were observed. Blood counts taken every other day were all normal; however, the sedimentation rate remained moderately rapid. Five blood transfusions of 250 c.c. each were given over a period of 2 weeks to correct the anemia.

The patient was observed in the hospital for an additional 9 days after oral penicillin had been discontinued, and blood cultures during this period were negative. She was discharged on May 21, 1945 and was examined every 2 weeks for the ensuing 8 months. The child was given complete freedom in her range of activities except for the avoidance of exhaustive play. A daily temperature reading was recorded. She has remained entirely afebrile, numerous blood counts have been normal, and 17 blood cultures obtained at intervals during this observation period of 8 months have consistently remained sterile. The sedimentation rate taken on July 23, 1945 was 22 mm. in 1 hour (Wintrobe method). She has gained 15 pounds in weight. A roentgenogram reveals no change in the cardiac dimensions.

Discussion

The clinical course of the case presented here has been summarized in chart 2. The striking defervescence of fever 8 hours after penicillin had been started and the prompt sterilization of the peripheral blood are to be noted. The patient received penicillin for an arbitrarily selected period of 14 days, during which time the suspected portal of entry, the decayed tooth, was removed. Clinically she was greatly improved and manifested a degree of well-being during the remainder of her hospital stay. At no time either during or following therapy were any embolic phenomena observed.

The sensitivity of the invading strain of Streptococcus viridans in this case ranged between 0.05 and 0.1 Florey units. In preliminary experiments previously cited[7, 8] the penicillin concentrations, obtained for a 3-hour period, when 100,000 units were ingested, produced levels that were considerably in excess of this susceptibility range. It was, therefore, decided to administer this dose every 3 hours, having reasonable assurance of constantly effective blood levels of penicillin. Chart 1 represents the resultant curves of penicillin assays obtained on 2 separate 6-hour periods, selected at random intervals while this patient was receiving the drug. It will be noted that the concentrations obtained ranged between 0.078 and 1.24

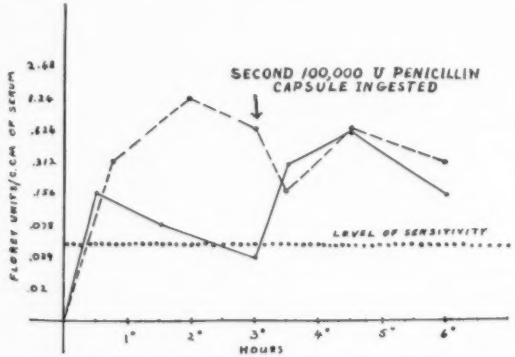

CHART 1. PENICILLIN BLOOD LEVELS OBTAINED ON THE PATIENT WHILE UNDER TREATMENT DURING 2 RANDOM 6-HOUR PERIODS AFTER ORAL ADMINISTRATION OF 100,000 UNITS EVERY 3 HOURS

Note the incremental rise in Penicillin titer after ingestion of 2nd capsule. The sensitivity level of the Streptococcus viridans is indicated, and, as can be observed, the penicillin blood levels usually substantially exceed the sensitivity level.

Florey units per c.c. except in one instance when the blood level was 0.039 Florey units per c.c. at the end of 3 hours. These levels were within or well above the susceptibility range of the invading organism.

Fourteen days were arbitrarily chosen as the period of treatment, to be varied by the clinical course and the repeated blood cultures. During this time a total dose of 11,200,000 units of penicillin was given, which is approxiately twice the total amount reported to have been administered to cases of subacute bacterial endocarditis when the parenteral method was employed (table 1). It is not possible to state whether or nor oral penicillin could have been discontinued before the 14-day period had been completed. In this regard it is of interest to note that the temperature became normal and the blood cultures negative 12 hours after treatment had been started.

The advantages of administering penicillin by mouth to cases of subacute bacterial endocarditis are especially manifest because of the length of time during which therapy must be maintained. Discomfort to the patient incurred by parenteral administration is thus avoided. When the intermittent intramuscular mode is employed a total of 200 to 300 separate injections are required and undoubtedly are a source of considerable physical and psychic trauma. Using the continuous intravenous method of giving penicillin, Loewe[3] observed a relatively high incidence of toxic reactions including thrombophlebitis, fever, chills, local pain and troublescome instances of regional angiitis. The danger of thrombophlebitis is especially real when this method is employed for the treatment of subacute bacterial endocarditis in view of the fact that thereapy is continued for 3

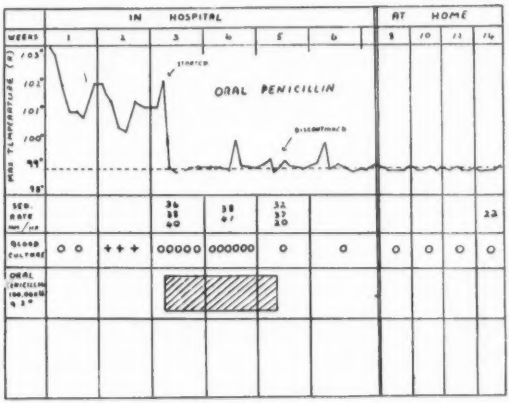

CHART 2. SUMMARY OF CLINICAL COURSE

to 5 weeks. Congestive heart failure is not an infrequent complication of endocarditis, and in such cases the administration of excessive amounts of fluid, entailed by the intravenous route, would be contraindicated.

The disadvantages of these parenteral routes are obviated when penicillin is given by mouth, and the management of cases of subacute bacterial endocarditis is definitely simplified for the hospital personnel.

No subjective or objective toxic manifestations were observed in this case.

The advisability of the use of heparin in conjunction with penicillin in the treatment of this disease is controversial. Dawson and Hunter[4] reported that 5 patients in their series received penicillin alone, and the results were thought to be as satisfactory as when heparin was used. Similarly, in the series of 9 cases reported by Meads et al.,[5] heparin was employed in only

3 patients and no essential variation in the 2 groups was noted. Loewe,[3] on the other hand, recommends the routine use of combined heparin-penicillin treatment for bacterial endocarditis. Because heparin has not been demonstrated to have any distinct advantage over penicillin alone and since its use is not without danger in view of its well known variable effect on the clotting time of the blood, it was not employed in our case.

Conclusions

1. The successful use of orally administered penicillin in the treatment of a case of subacute bacterial endocarditis is reported.

2. The dosage consisted of 100,000 units of powdered sodium penicillin in a double gelatin capsule every 3 hours for 14 days, totaling 11,200,000 units.

3. No subjective or toxic symptoms were noted.

4. In a follow-up period of 8 months the patient has remained afebrile, has shown persistently sterile blood cultures, and has been completely asymptomatic. It would seem reasonable to conclude that a cure has been achieved.

5. The definite advantages of oral penicillin for this disease are manifest because of the comparative ease of administration.

The authors wish to express their appreciation to Drs. Joseph Wall and E. Clarence Rice of the Medical Research Committee of Children's Hospital, Washington, D. C., for their helpful suggestions and advice and to Miss Betty Porter for her technical assistance.

BIBLIOGRAPHY

1. Keefer, C. S., and others: Penicillin in treatment of infections; report of 500 cases. J. A. M. A., 1943, **122**, 1217.
2. Loewe, L., Rosenblatt, P., Greene, H. J., and Russell, M.: Combined penicillin and heparin therapy of subacute bacterial endocarditis; report of seven consecutive successfully treated patients. Ibid., 1944, **124**, 144.
3. Loewe, L. Combined use of anti-infectives and anticoagulants in the treatment of subacute bacterial endocarditis, Bull. New York Acad. Med., 1945, **2**, 59.
4. Dawson, H., and Hunter, T. H.: Treatment of subacute bacterial endocarditis with penicillin. J. A. M. A., 1945, **127**, 129.
5. Meads, M., Harris, H. W., Finland, M.: Treatment of bacterial endocarditis with penicillin. New England J. Med., 1945, **232**, 463.
6. Paullin, J. E., and McLoughlen, C. J.: Treatment of subacute bacterial endocarditis with penicillin. Ann. Int. Med., 1945, **22**, 475.
7. Spink, W. W., and Hall, W. H.: Penicillin therapy at University of Minnesota hospitals, 1942–1944. Ibid., 1945, **22**, 510.
8. Burke, F. G., Ross, S., and Strauss, C. S.: Oral administration of penicillin; preliminary report. J. A. M. A., 1945, **128**, 83.
9. Ross, S., Burke, F. G., and McLendon, P. A. Penicillin by mouth: a clinical trial. J. A. M. A., 1945, **129**, 327.
10. Rammelkamp, C. H.: Method of determining the concentration of penicillin in body fluids and exudates. Proc. Soc. Exper. Biol. & Med., 1942, **51**, 95.

MACROCYTIC ANEMIA TREATED WITH FOLIC ACID

Case Report No. 47

Dr. Howard Topley and Dr. Frances Ayres M. P. 39-3383

M. P., a 7 year old colored male, has had ten previous admissions to Children's Hospital because of marked anemia. He was first admitted at the age of 8 months with the chief complaint of cough of one month's duration. The parents gave a history of having six children between the ages of six and eighteen months who died because of "weakness." Physical examination at this time revealed a very pale, poorly nourished, and acutely ill child. The conjunctiva and throat were pale, the right ear drum was inflamed and there was a marked rhinorrhea. On the third hospital day petechiae appeared on the arms and legs and on the seventh day the child bled from two small ulcerated areas on the tongue and developed a diarrhea. The buccal mucosa and the tongue continued to ulcerate, and on the eleventh day hemorrhage from the bowel occurred. On the twenty-second hospital day a spontaneous hemorrhage occurred into the right knee joint.

Laboratory examination revealed gross hematuria on two occasions and occult blood in the stools once.

Hemogram showed 3.8 gms. of hemoglobin with 820,000 red blood cells; the white cell count was 7,800 with 17% neutrophiles, 15% segmented forms, 2% stab forms, 64% lymphocytes and 19% unclassified. Thrombocyte count was 15,000. The coagulation time was 3½ minutes and bleeding time 1 minute. Two sickling tests showed 10% sickling. A sternal puncture showed a marked reduction in the erythroblastic elements and a hyperplasia of the myeloid elements.

X-ray of the chest the day after admission showed considerable cardiac enlargement to the left with some suggestion of congestion of the lungs. X-ray of the long bones was negative.

He was treated with multiple blood transfusions, liver, iron and vitamin therapy. The hemoglobin and red blood count approached normal values and the patient was discharged much improved.

At the age of 29 months, he was re-admitted to the hospital because of a cold, listlessness, anorexia and weakness. The significant findings on physical examination were marked pallor, an enlargement of the liver down to the iliac crest, an apical systolic murmur and edema of the lower extremities.

The hemogram was essentially the same as on the previous admission. The Kahn was negative, and the total serum protein, fragility tests, icterus index, blood cholesterol, serum phosphorous and calcium were within normal limits.

X-ray of the long bones and skull showed definite changes with marked disturbances in trabeculation and mineralization. X-ray of the chest showed the heart to be markedly enlarged to the left.

The hospital course was one of moderate improvement under a similar therapeutic regime as on his previous admission.

The child was again admitted at the age of four years. On physical examination he appeared pallid and apathetic and showed a moderate degree of jaundice and cervical lymphadenopathy. The liver was palpable two fingers below the costal margin.

Hemogram revealed a moderate degree of anemia but was otherwise not remarkable. The tuberculin test was strongly positive for the first time; however, five consecutive stomach washings were negative for TBc. Urine examinations and bleeding and coagulation times were within normal limits. No sickling of the red blood cells was noted. Icterus index was 17; sedimentation rate was 8 mm./hr.; stool and blood cultures and agglutination tests were negative. The ECG was normal. X-ray of the chest revealed moderate cardiomegaly and the lungs showed considerable increase in fibrosis.

The child was re-admitted at the age of 5 years for hospital stays of 11 and 18 days respectively, these being his fourth and fifth admissions. There was no change in his laboratory or clinical course. A 30% sickling was noted on one occasion.

On his sixth admission at the age of 6 years a splenectomy was performed. The pathological report of the spleen was as follows: "the gross weight was 40 gms.; the surface was slate gray and slightly roughened due to fibrous adhesions. The cut surface was deep red and showed an increase in fibrous tissue elements. On microscopic examination it contained the usual elements of bone marrow with each type well represented. The striking feature was the abundance of eosinophilic leucocytes. These, like the neutrophiles, were noted in various stages of development. A number of cells with granules were probably endothelial in character."

On his seventh admission, he developed abdominal enlargement suggestive of ascites. Total protein determinations at this time ranged from 6.35 to 8.63 gms.%. The Van den Bergh, cephalin flocculation, and blood cultures were negative.

Extensive laboratory and diagnostic procedures were performed in an effort to classify this child's anemia and to determine its etiology. His diet, eating habits and gastrointestinal history were carefully investigated, but were noncontributary. There was no consistent chronic bleeding or conclusive evidence of excessive hemolysis. No agent productive of a depression of the bone marrow could be indicted. On the basis of the ster-

nal marrow picture, a diagnosis of hypoplastic, macrocytic anemia of undetermined etiology had been made.

Treatment in the past had consisted of blood transfusions augmented by liver injections, iron and vitamins. His reticulocyte count had never responded to adequate liver therapy. He was usually discharged with a red count of approximately 3,000,000 only to return 6 months or so later with a million or less red cells. Splenectomy, performed more or less empirically, proved to be of no lasting value.

He was admitted again on February 4, 1946 for treatment with folic acid. His red blood cell count on admission was 1,800,000 with a hemoglobin of 5.5 gms.; white cell count was 2,400 with 48% neutrophils, 40% lymphocytes and 11% unclassified. The thrombocyte count was 10,000. Treatment during this admission has consisted only of folic acid in the doses noted on the accompanying chart. The marked response of the red blood cells, hemoglobin and reticulocytes is to be noted. Smears have revealed a consistent macrocytosis of the red blood cells with nucleated red blood cells up to 12,000/cu.mm., and normoblasts. Clinically he has shown marked improvement with a noticeable increase in appetite and activity.

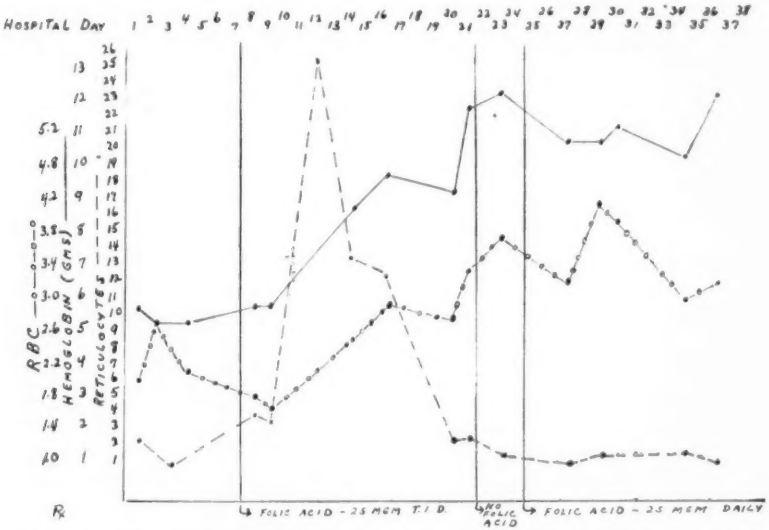

CHART 1.—Illustrating the response of the reticulocyte count, hemoglobin and red count following the institution of folic acid therapy. The striking reticulocyte count response is to be particularly noted.

Discussion

E. Clarence Rice, M.D.

This patient has been under observation for the past six years, during which time his anemia has been given various diagnoses, the most recent one being hypoplastic anemia. Instead of being a normocytic normochromic type, it is of the macrocytic hypochromic type. The hypoplastic anemia is considered to be normocytic and normochromic. The patient's blood varies greatly at times, microcytes being numerous on occasion, macrocytes at others. Target cells have been observed. The occasional fall of the thrombocytes and leucocytes to low levels indicate that all of the cellular elements of the bone marrow may at times be involved. While a recent bone marrow examination has not been made, the previous findings revealed a reduction in the number of the cells of the erythroblastic series. The presence of reticulocytes at times in normal or somewhat increased number indicate that the marrow is capable of responding with the production of erythrocytes in increased amount. At times they have practically disappeared from the peripheral blood.

One remarkable feature has been the low level to which the red blood cell count and hemoglobin concentration can fall and the patient survive. Counts under one million with hemoglobin values between 2 and 3 grams per cent have been obtained several times and on November 15, 1944, a report was made of less than 109,000 erythrocytes with hemoglobin of approximately 1 gram per cent. The patient seems to have developed a tolerance to his profound anemia and does not exhibit a disability comparable to it.

This boy's anemia is quite similar to that seen in the Mediterranean type of anemia. While the disease is seen almost exclusively in those persons having their origins from those originally coming from the Mediterranean basin, there seems to be no reason why a similar disease could not appear in those who stemmed from other sources. Further examination of the bones and bone marrow this patient should be made. The family should be further investigated.

Macrocytic anemias are not common in children. Those of the hyperchromic variety usually respond to the parenteral administration of liver extract. No evidence of hepatic disease has been established; however, his gastro-intestinal tract has been insufficiently studied. One gastric analysis indicated an absence of free hydrochloric acid. He received liver extract by intramuscular injection without evident response. The removal of the spleen was followed by a short period of improvement.

We have been surprised and pleased by the rather prompt response in all of the cellular elements of the blood following the administration of syn-

thetic L. Casei factor.* The rise in the number of reticulocytes to 26 per cent on the fifth day after the administration of the drug with subsequent increase in erythrocytes and hemoglobin had never been observed previously in this patient as a result of other treatment. The fact that it has been possible to maintain the patient's blood at a fairly satisfactory level leads us to feel that an effective therapeutic aid has been found for this patient. Whether or not the gains that he has made can be maintained remains to be seen.

Recently an increasingly voluminous literature has been appearing concerning folic acid. It appears that this substance is a member of the vitamin B complex and is similar or identical to vitamin Bc, an antianemic factor for the chick. With *Streptococcus lactis R* as the test organism, assays have shown that liver, kidney, mushroom, yeast and especially green leaves and grass contain the compound in abundance.[1, 2] It has been designated as "folic" (folium, leaf) acid.[1] It does not appear that the *L. casei* factor and the antipernicious anemia factor are the same.

Apparently, the terms factor U, the chick growth factor, vitamin B_c, folic acid and *L. casei* factor are identical or very closely related. It is probable that vitamin M is a somewhat similar substance. Recently the synthesis of a compound identical with *L. Casei* factor has been attained.[3]

The synthetic preparation has been used in the treatment of this patient. It appears to be of value in the treatment of nutritional macrocytic anemias[4] such as sprue and it has been suggested that it may have some activity as an antipernicious anemia substance.[5] In addition, it has been reported to be a strong inhibitor of tumor growth in mice.[6]

The fact that it has been possible to break down the vitamin B complex further and isolate and prepare synthetically a substance which is of value in the treatment of anemia, represents a great step forward.

REFERENCES

(1) Mitchell, H. K., Snell, E. E., and Williams, R. J.: J. A. Chem. Soc. **63:** 2284 (1941).
(2) Mitchell, H. K., and Snell, E. E.: Univ. of Texas Publication No. 4137 36 (1941).
(3) Angier, R. B., et al., and Cosulich, D. B., et al.: Science **102:** 227 (1945).
(4) Spies, T. D., Vilter, C. F., and Koch, M. D.: South. M. J. **38:** 707 (1945).
(5) Moore, C. V., Bierbaum, O. S., Welch, A. D., and Wright, L. D.: J. Lab. Clin. M. **38:** 1056 (1945).
(6) Woolley, D. W., and Sprince, H. J.: J. Biol. Chem. **153:** 687 (1944).

* Folvite (synthetic folic acid) furnished by Lederle Laboratory, Inc., Pearl River, N. Y. by Stanton M. Hardy, M.D.

SUDDEN DEATH FROM CORONARY INSUFFICIENCY: REPORT OF A CASE IN AN INFANT

Case Report No. 48

Dr. Clifford J. Tichenor D. M. 46-622

This brief report of the sudden unexplained death of a four month old infant is made because it may contribute to knowledge of the causes of sudden unexplained death in infancy. It is possible that if all the possibilities were explored more carefully, status thymicolymphaticus would be listed less freqeuently than it is now as a cause of death. Only postmortem examination of the heart will establish the final diagnosis of such cases as presented here. According to Potter and Adair the cause of 57% of deaths of newborn infants is not verified by pathological examination.

Report of Case

D. M., a four months old white female, was admitted to Children's Hospital because of poor weight gain and malnutrition. The delivery was full term and normal; forceps were applied at the outlet after a labor of seven hours duration. The child's weight at birth was 3000 gms. The infant appeared well developed and vigorous at birth with a normal cry, well aerated lungs and good color. Breast feedings were instituted postpartem and the infant nursed well for the first month. The initial weight loss was slight until the fourth day at which time the weight curve began to rise. Bowel movements were regular and the temperature remained within normal limits. There was no vomiting or diarrhea during this first month. Orange juice and cod liver oil were started at the beginning of the second month.

The infant gained six ounces (180 gm.) a week for the first two months, but then began to become constipated and had several moderately severe episodes of diarrhea. Multiple changes of formula were tried, but the infant's third month was characterized by failure to gain weight. There were also several episodes of vomiting. The fourth month was also punctuated by further unsatisfactory changes of formulas and a stationary weight curve.

The infant was admitted to the hospital on January 24, 1946, weighing 4710 gm. She appeared poorly nourished, underdeveloped, undersized and rather pale, the general appearance being that of a chronically ill child. The temperature was 98.6°. During the initial examination the infant appeared very irritable and cried as though she were in severe pain. A moderate elevation deformity of the entire left hemithorax together with costochondral knobbing was noted. The left border of the heart was per-

cussed at the left anterior axillary line but no murmurs were heard. The chest circumference was slightly less than that of the head. The infant was hardly able to hold her head erect when the trunk was supported. She seemed to recognize her mother and grasped at objects.

Urinalysis was negative. Blood count showed the hemoglobin to be 12 gm. with 4,140,000 erythrocytes; leucocytes were 6,600 with a normal distribution of neutrophiles and lymphocytes. The stained smears showed no abnormalities. Urine culture grew Aerobacter aerogenes. The spinal fluid was normal. X-ray examination of the long bones of the upper and lower extremities revealed no evidence of abnormality.

The initial hospital formula consisted of evaporated milk, with added lactic acid. Adjuvant vitamin supplements included cod liver oil, ascorbic acid and Vitamin B complex. On the fourth day 50 c.c. of plasma in 25 c.c. normal saline was given subcutaneously.

By the evening of the fourth day the temperature had risen to 101° and there was a moderate swelling and redness over the sites of the subcutanous clyses on the back. Urinalysis and blood count were again essentially normal. The infant's breathing now became somewhat labored, associated with flaring alae nasi and costal retraction. The breath sounds were clear, the heart rate was rapid and regular. A questionable apical systolic murmur was heard by one observer at this time. The infant was crying continuously as if in pain and became slightly cyanotic. Continuous oxygen was administered.

On the fifth morning the cyanosis had shown slight improvement. The point of maximum intensity of the heart beat was now at the anterior axillary line. Hyperresonance was elicited over the right lung field and decreased to absent breath sounds were present over the upper left anterior chest. In view of the acute onset of dyspnea, apparent pain, cyanosis, and chest findings, a diagnosis of left sided atelectasis was entertained. X-ray of the chest at this time revealed some disseminated infiltration throughout the right lung indicative of broncho-pneumonia. The heart was greatly enlarged and displaced to the left, probably indicative of scattered areas of atelectasis of the left lung.

By the sixth day the infant's condition was critical; respirations became more rapid and labored and the patient expired suddenly.

Necropsy was performed. The heart weighed 100 gm. (normal 27 gm.). The left ventricle showed considerable dilatation and hypertrophy. The anterior surface of the left ventricle showed what appeared to be irregular thickenings of the epicardium and there seemed to be evidence of fibrosis or degeneration of the myocardium corresponding to this. The myocardium was soft and reddened. The endocardium of the left ventricle had

a whitish fibrous appearance, certain portions having a bluish cyanotic tinge. The left coronary artery arose from the medial cusp of the pulmonary artery, its course being normal. The right coronary artery arose and coursed normally. Just medial to the ostium of the right coronary artery there was an anomalous ostium, small and slit like, which gave rise

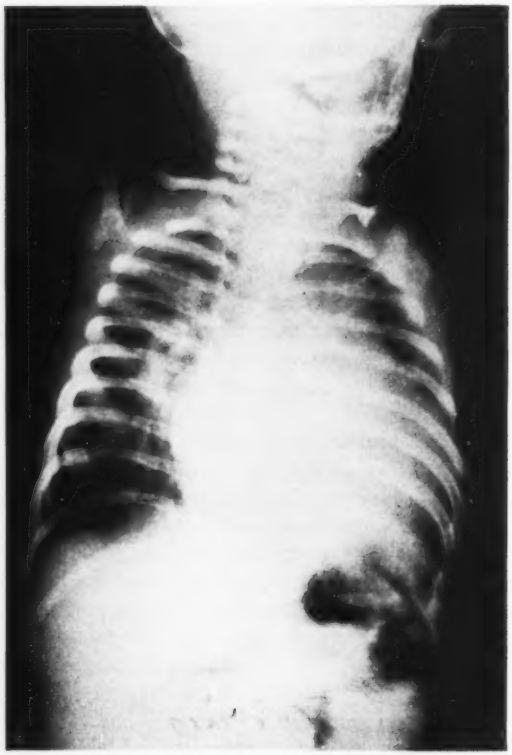

FIG. 1. X-RAY OF THE CHEST SHOWING MARKED CARDIAC ENLARGEMENT

to an anomalous vessel which could be probed for a distance of less than one centimeter in the direction of the pulmonary valve.

The anterior two thirds of the right lung were reddish and moderately congested while the posterior third was dark purple and firm. The left lung was almost entirely atelectatic and the tissue was firm and non-crepitant. The pathological diagnosis was: Pulmonary congestion; atelectasis, left; developmental anomaly of the heart, origin of the left

coronary artery from the pulmonary artery, hypertrophy and dilatation of the left ventricle and myocardial fibrosis and degeneration.

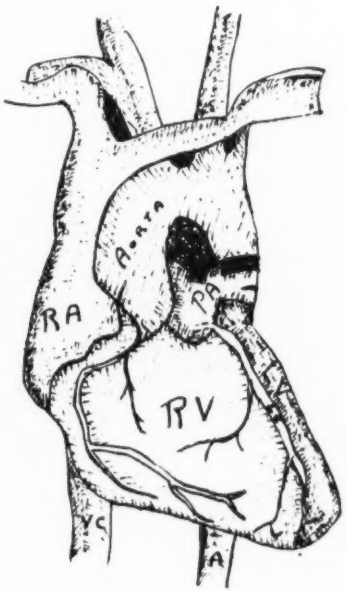

FIG. 2. DIAGRAM ILLUSTRATING THE ANOMALOUS ORIGIN OF THE LEFT CORONARY ARTERY FROM THE MEDIAL CUSP OF THE PULMONARY ARTERY

DISCUSSION

The coronary vessels were inadequate in this case, the left coronary vessel supplying most of the left ventricle with unoxygenated blood, since it arose from the pulmonary artery. This inadequacy had resulted in gross and microscopic changes in the myocardium.

It is interesting to note that at the Mayo Clinic since 1922, some type of anomaly of the coronary vessels has been encountered in fifty-five cases in which necropsy was performed. In three cases two anomalies were present. In twenty-eight of these cases accessory coronary orifices were found; in eleven aplasia or absence of the right coronary artery, in four aplasia and absence of the left coronary artery; in nine distinct abnormality

in the position of the origin of the coronary arteries, and in three absence of the left circumflex branch. In one case stenosis of the left coronary was present while in another the right coronary arose from the pulmonary artery. In a third case in which a single arterial trunk was associated with a single ventricle, the aortic coronary openings were absent but the right coronary artery arose from the carotid artery. Absence or other congenital anomalies of the coronary vessels do not necessarily entail death, for the ages of the patients in this group when death occurred varied from four days to seventy-nine years. In none of the fifty-five cases was the coronary disease considered responsible for the death.

According to Knop of the Mayo Clinic, the significance of anomalous coronary arteries therefore does not lie in the coronary arteries themselves but in the coronary insufficiency and changes in the myocardium which result. Even if one of the coronary arteries is absent and compensation is made by the persisting vessels, the anomaly is compatible with life.

In the case of this infant, congenital origin of the left coronary from the pulmonary artery with an inadequate left branch from the right coronary artery resulted in fibrosis and degeneration of the myocardium and sudden death. Myocardial ischemia with resulting angina probably accounted for the manifestations of pain which this infant appeared to experience premortem.

In any instance of "idiopathic" cardiac enlargement without a murmur, the possibility of an anomalous origin of the coronary artery should be considered in the differential diagnosis.

REFERENCES

Knop, C. Q., M.D., and Bennet, W. A., M.D., Sudden Death from Coronary Insufficiency; Staff Meetings of the Mayo Clinic, December 13,1944.

CLINICO-PATHOLOGICAL CONFERENCE

Directed by Dr. E. Clarence Rice
Assisted by Dr. Robert B. Sullivan

Case Report No. 49

Dr. Robert B. Sullivan C. B. 45-10349

A six year old white boy entered the hospital on December 27, 1945 because of a headache, stiff neck, and drowsiness of two days' duration. He had been in good health until one week before admission when he developed an upper respiratory infection. During the two days preceeding his admission he had several severe occipital headaches. Careful questioning revealed that there had been no headaches or other evidence of abnormality before this illness. Past history and family history were noncontributary.

He was an acutely ill boy with hot skin, malar flushing, and a temperature of 103°. There were no petechiae and the eyes, ears, nose, and throat were negative. Nuchal rigidity was 4 plus and there was a 3 plus Kernig's sign. No other abnormal reflexes were elicited. The lungs, heart, and abdomen were negative. A spinal tap showed turbid fluid which contained 485 leucocytes per cu.mm. with 83% polymorphonuclears, 15% lymphocytes and 2% monocytes; there was 25 mgm. % protein and 40 mgm.% sugar. Identification of organisms was somewhat equivocal on smear but there were two gram positive cocci which were suggestive of pneumococci. There was no growth produced on the culture media. The red blood cell count was 3,800,000 per cu.mm. with 12 grams of hemoglobin. The white blood cell count was 16,200 with 83% polymorphonuelcears, 1% band forms, 13% lymphocytes, 1% eosinophiles and 2% monocytes. Except for a 1 plus acetone the urine was normal.

Five thousand units of penicillin were instilled intrathecally on each of the first two days of hospitalization and 30,000 units were infected intramuscularly every two hours. Two grams of sodium sulfadiazine in 100 c.c. of 5% glucose in saline were given by clysis every six hours. He received 2.75 grams of sodium bicarbonate by mouth every six hours.

On the second day the spinal fluid was slightly more turbid and contained 1,425 leucocytes per cu.mm. with 92% polymorphonuclears and 8% lymphocytes. The protein was 45 mgm.% and the sugar 35 mgm.%. No organisms were seen and the culture was again sterile. Clinically his appearance was definitely encouraging. The temperature decreased slowly from 103° on admission to 101° on the third day. His pulse was in proportion to the fever. At this time he began to complain of a severe occipital headache. Because the etiologic agent was not definitely established

he was given two ampoules of anti-hemophilus serum intramuscularly at 3:00 P.M. on the third day. At 5:50 P.M. he was given a soap suds enema and forty-five minutes later, while lying on the bed pan, he coughed, became cyanotic and stopped breathing. Both eyes were widely dilated, round, and equal. He was seen by a resident within three minutes and pronounced dead.

FIG. 1. ILLUSTRATING THE SIZEABLE HEMORRHAGE OVER THE INFERIOR ASPECT OF THE CEREBELLUM AND BRAIN STEM

Autopsy summary: The body was well devloped and nourished with no external evidences of abnormality other than widely dilated, round, equal pupils. Bloody fluid was obtained on cisternal tap. When the dura was incised, a moderate amount of fluid blood was found over the superior suface of the brain, and the superficial vessels were markedly engorged. Covering the inferior aspect of the cerebellum and all of the brain stem was a large amount of freshly clotted blocd and when this was removed there was disclosed an oval shaped, smooth, gray cystic mass which measured

3.5 by 2.5 by 1.5 centimeters. It was in the mid-line, touched both cerebellar lobes laterally and pressed into the medulla posteriorly. Anteriorly it rested upon the clivus which was slightly eroded. Superiorly and inferiorly there arose from the mass vessels having the calibre of the normal basilar artery. On the left side of the mass there was a discontinuity of its surface through which clotted blood protruded. Incision of the corpus callosum disclosed clotted blood in the third and both lateral ventricles. No evidence of an exudate was seen but smears made from the brain surface revealed a moderate number of gram positive diplococci morphologically resembling pneumococci. Cultures produced only Pseudomonas aeruginosa. Other findings of interest were marked pulmonary congestion and edema and a moderate number of atheromatous placques just above the aortic ring.

Pathological diagnosis: Pyogenic Meningitis—probably Pneumococcal. Congenital aneurysm of the basilar artery, ruptured.

Discussion

Ruptured aneurysm of a cerebral artery is a rare cause of death in childhood. The case reported above is the second in the records of Children's Hospital. In the first case, a nine year old white girl with no prodromal symptoms, was found comatose in bed, the aneurysm having ruptured during her sleep. The left pupil was dilated, cysnosis was marked, and pink, frothy fluid flowed continuously from her nose and mouth. Five hours later she was dead. Autopsy disclosed a ruptured aneurysm (1.5 cm. in diameter) of the anterior communicating artery. Pulmonary edema was marked.

"Spontaneous" subarachnoid hemorrhage accounts for two per cent of all sudden deaths and rupture of a congenital aneurysm is by far the most frequent pathogenesis. In 1887 Eppinger[2] first employed the term "berry" aneurysms because of their shape and color. Most of them are between 3 and 10 millimeters in diameter but they may be as large as 4 by 4 centimeters. They are usually on the circle of Willis or its main branches and are usually at or near the bifurcations. Some are multiple and they may be incidental findings at autopsy. Forbus[1] in 1930 demonstrated a lack of the muscular coat at the site of the sacculation and posulated the degeneration of the intimal elastica due to continual stretching. Berry aneurysms usually rupture spontaneously but some rupture during effort wherein the glottis is closed and the blood pressure is raised. Toxic, infectious and degenerative diseases are frequently inciting factors but trauma is rarely related. One ruptured aneurysm was recently reported in the U. S. Naval Medical Bulletin[4] following a typhoid-tetanus booster injection.

The diagnosis is rarely made before rupture occurs. In the classical

case a healthy individual with or without premonitory headaches suddenly cries out because of severe headache, and soon becomes comatose with stertorous breathing. The pupils may be dilated, the pulse slow and perhaps irregular. The temperature usually rises and nuchal rigidity and Kernig's sign are often present. Patellar reflexes are diminished or absent and there is frequently a positive Babinski. There are often retinal hemorrhages and sometimes convulsions. The spinal fluid is uniformly bloody and under increased pressure. The supernatant fluid is xanthochromic. If death does not ensue consciousness returns slowly, usually within twenty-four hours. There is a severe headache, photophobia and signs of meningeal irritation. In those that survive, serious neurological residual or headaches are not common after two months. There are conflicting reports concerning the rate of survival following a ruptured aneurysm. However, concerning subarachnoid hemorrhages as a group, the most recent review[3] concludes that about 30 per cent will die in the initial attack and another 20 per cent will die in subsequent attacks. The majority of recurrences are during the first month. Therefore if neurosurgical ligation is to prevent death from a recurrence it myst be employed early. Thereafter the mortality from craniotomy is greater than that from recurrence. Localization of an aneurysm is accomplished mainly by arteriograms but aided by neurological signs and x-rays which in some instances show bone erosion or cresentic shadows due to calcium in the wall of aneurysm (Abbl's rings).

The precipitating cause of the ruptured aneurysm in this case is somewhat indeterminate. It could have conceivably been due to a weakening of the walls of the sacculated aneurysm by the co-existing meningitis. Another possible cause may have been the sudden change in the dynamics within the subarachnoid space due to the two spinal punctures performed prior to death.

REFERENCES

(1) Forbus, W. D.: On the Origin of Miliary Aneurysms of the Superficial Cerebral Arteries. Bull. Johns Hopkins Hosp., **47:** 239, 1930.

(2) Eppinger quoted by Martland, H. S.: Spontaneous Subarachnoid Hemorrhage and Congenital "Berry" Aneurysms of the Circle of Willis. Am. J. Surg., **43:** 10, 1939.

(3) Wolf, G. A., Goodell, H., Wolff, H. G.: Prognosis of Subarachnoid Hemorrhage. J. A. M. A., **129:** 715, 1945.

(4) Berlin, R. B.: Ruptured Aneurysm Following Typhoid-Tetanus Booster Injection. U. S. Naval Bull., **44:** 391, 1945.

(5) Courville, C. B.: Pathology of the Central Nervous System. Pacific Press Publishing Association, 1945.